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77 Rogot E, Murray JL. Smoking and causes of death among US veterans: 16 years of observation. *Public Health Rep* 1980;95:213-22.
78 Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *BMJ* 1976;2:1525-36.
79 Iso H, Shimamoto T, Sato S, Koike K, Iida M, Komachi Y. Passive smoking and plasma fibrinogen concentrations. *Am J Epidemiol* 1996;144:1151-4.
80 Howard G, Burke, GL, Szklo M, Tell GS, Eckfeldt J, Evans G, et al. Active and passive smoking are associated with increased carotid wall thickness. *Arch Intern Med* 1994;154:1277-82.
81 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
82 Schmid P, Katanikas G, Kritz H, Pirich C, Stamatopoulos Y, Peskar B, et al. Passive smoking and platelet thromboxane. *Thromb Res* 1996;81:451-60.
83 Di Minno G, Silver MJ, Murphy S. Monitoring the entry of new platelets into the circulation after ingestion of aspirin. *Blood* 1983;61:1081-5.
84 Wells AJ. Post-hearing comment re OSHA hearing: meta-analysis of relative risk of heart disease from ETS exposure in the workplace. Washington, DC: US Department of Labor, 1995. (Docket H-122, Docket Office Room N-2625.)
85 Prentice RC, Carroll R, Scanlon PJ, Thomas JX. Recent exposure to cigarette smoke increases myocardial infarct size. *J Am Coll Cardiol* 1989;13:124A.
86 Zhu B, Sun Y, Sievers RE, Glantz SA, Parmley WW, Wolfe CL. Exposure to environmental tobacco smoke increases myocardial infarct size in rats. *Circulation* 1994; 89:1282-90.
87 Zhu B, Sun Y, Sievers RE, Shuman JL, Glantz SA, Chatterjee K, et al. L-arginine decreases infarct size in rats exposed to environmental tobacco smoke. *Am Heart J* 1996;132:91-100.
88 Penn A, Snyder CA. Inhalation of sidestream cigarette smoke accelerates development of arteriosclerotic plaques. *Circulation* 1993;88:1820-5.
89 Penn A, Chen L-C, Snyder CA. Inhalation of steady-state sidestream smoke from one cigarette promotes arteriosclerotic plaque development. *Circulation* 1994;90:1363-7.
90 Zhu B-Q, Sun Y-P, Sievers RE, Isenberg WM, Glantz SA, Parmley WW. Passive smoking increases experimental atherosclerosis in cholesterol-fed rabbits. *J Am Coll Cardiol* 1993;21:225-32.
91 Sun Y-P, Zhu B-Q, Sievers RE, Glantz SA, Parmley WW. Metoprolol does not attenuate atherosclerosis in lipid-fed rabbits exposed to environmental tobacco smoke. *Circulation* 1994;89:2260-5.
92 Roberts KA, Rezai AA, Pinkerton KE, Rutledge JC. Effect of environmental tobacco smoke on LDL accumulation in the artery wall. *Circulation* 1996;94:2248-53.
93 Wald NJ, Idle M, Boreham J. Serum cotinine levels in pipe smokers: evidence against nicotine as cause of coronary heart disease. *Lancet* 1981;2:775-7.
94 Wald NH, Watt HC. Prospective study of effect of switching from cigarettes to pipes or cigars on mortality from three smoking related diseases. *BMJ* 1997;314:1860-3.

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The accumulated evidence on lung cancer and environmental tobacco smoke

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See editorial by Davis and p 973

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Abstract

Objective: To estimate the risk of lung cancer in lifelong non-smokers exposed to environmental tobacco smoke.

Design: Analysis of 37 published epidemiological studies of the risk of lung cancer (4626 cases) in non-smokers who did and did not live with a smoker. The risk estimate was compared with that from linear extrapolation of the risk in smokers using seven studies of biochemical markers of tobacco smoke intake.

Main outcome measure: Relative risk of lung cancer in lifelong non-smokers according to whether the spouse currently smoked or had never smoked.

Results: The excess risk of lung cancer was 24% (95% confidence interval 13% to 36%) in non-smokers who lived with a smoker ($P < 0.001$). Adjustment for the effects of bias (positive and negative) and dietary confounding had little overall effect; the adjusted excess risk was 26% (7% to 47%). The dose-response relation of the risk of lung cancer with both the number of cigarettes smoked by the spouse and the duration of exposure was significant. The excess risk derived by linear extrapolation from that in smokers was 19%, similar to the direct estimate of 26%.

Conclusion: The epidemiological and biochemical evidence on exposure to environmental tobacco smoke, with the supporting evidence of tobacco specific carcinogens in the blood and urine of non-smokers exposed to environmental tobacco smoke, provides compelling confirmation that breathing other people's tobacco smoke is a cause of lung cancer.

Introduction

Ten years ago scientific committees and national organisations concluded that exposure to environmental tobacco smoke (also called passive smoking) is a cause of lung cancer.[1-4] Substantial additional evidence has since been published, and we report a new analysis. The additional data permit a more precise estimate of the size of the association, with a further assessment of whether it is cause and effect by seeking a dose-response relation and examining whether sources of bias and confounding could account for the association. We also compared the direct estimate of risk from epidemiological studies with that from a low dose linear extrapolation of the risk in smokers using biochemical markers of exposure to tobacco smoke.

As before,[5] the estimate of effect was the relative risk of lung cancer in lifelong non-smokers according to whether the spouse currently smoked or had never smoked. Spousal exposure is the best available measure: it is well defined and has been validated using biochemical markers.[6-9] It reflects exposure in general because non-smokers who live with smokers tend to be more exposed to tobacco smoke from other sources, because they are more likely to mix socially with smokers.[6] Workplace exposure varies considerably and is difficult to measure.

Methods

Direct estimate of risk of lung cancer from epidemiological studies

Studies of environmental tobacco smoke and lung cancer were identified from Medline, the citations in each study, and consultation with colleagues. We

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Table 1 Epidemiological studies of the risk of lung cancer in lifelong non-smokers whose spouses smoked relative to the risk in those whose spouses did not smoke

		Women			Men		
Study	Year, country	Lung cancer cases	Controls	Relative risk (95% confidence interval)	Lung cancer cases	Controls	Relative risk (95% confidence interval)
Case-control sudies							
Chan et al[11]	1982, Hong Kong	84	139	0.75 (0.43 to 1.30)			
Correa et al[12]	1983, USA	22	133	2.07 (0.81 to 5.25)	8	180	1.97 (0.38 to 0.32)
Trichopolous et al[13]	1983, Greece	62	190	2.13 (1.19 to 3.83)			
Buffler et al[14]	1984, USA	41	196	0.80 (0.34 to 1.90)	11	90	0.51 (0.14 to 1.79)
Kabat et al[15]	1984, USA	24	25	0.79 (0.25 to 2.45)	12	12	1.00 (0.10 to 5.07)
Lam[17]	1985, Hong Kong	60	144	2.01 (1.09 to 3.72)			
Garfinkel et al[18]	1985, USA	134	402	1.23 (0.81 to 1.87)			
Wu et al[19]	1985, USA	29	62	1.20 (0.50 to 3.30)			
Akiba et al[20]	1986, Japan	94	270	1.52 (0.87 to 2.63)	19	110	2.10 (0.51 to 8.61)
Lee et al[21]	1986, UK	32	66	1.03 (0.41 to 2.55)	15	30	1.31 (0.38 to 4.52)
Koo et al[22]	1987, Hong Kong	86	136	1.55 (0.90 to 2.67)			
Pershagen et al[23]	1987, Sweden	70	294	1.03 (0.61 to 1.74)			
Humble et al[24]	1987, USA	20	162	2.34 (0.81 to 6.75)			
Lam et al[25]	1987, Hong Kong	199	335	1.65 (1.16 to 2.35)			
Gao et al[26]	1987, China	246	375	1.19 (0.82 to 1.73)			
Brownson et al[27]	1987, USA	19	47	1.52 (0.39 to 5.96)			
Geng et al[28]	1988, China	54	93	2.16 (1.08 to 4.29)			
Shimizu et al[29]	1988, Japan	90	163	1.08 (0.64 to 1.82)			
Inoue et al[30]	1988, Japan	22	47	2.55 (0.74 to 8.78)			
Kalandidi et al[33]	1990, Greece	90	116	1.62 (0.90 to 2.91)			
Sobue[34]	1990, Japan	144	731	1.06 (0.74 to 1.52)			
Wu-Williams et al[35]	1990, China	417	602	0.79 (0.62 to 1.02)			
Liu et al[37]	1991, China	54	202	0.74 (0.32 to 1.69)			
Jockel[39]	1991, Germany	23	45	2.27 (0.75 to 6.82)	9	70	2.68 (0.56 to 12.36)
Brownson et al[39]	1992, USA	431	1166	0.97 (0.78 to 1.21)			
Stockwell et al[40]	1992, USA	210	301	1.60 (0.80 to 3.00)			
Du et al[41]	1993, China	75	128	1.19 (0.66 to 2.13)			
Liu et al[10]	1993, China	38	69	1.66 (0.73 to 3.78)			
Fontham et al[43]	1994, USA	651	1253	1.26 (1.04 to 1.54)			
Kabat et al[44]	1995, USA	67	173	1.10 (0.62 to 1.96)	39	98	1.63 (0.69 to 3.85)
Zaridze et al[45]	1995, Russia	162	285	1.66 (1.12 to 2.45)			
Sun et al[46]	1996, China	230	230	1.16 (0.80 to 1.69)			
Wang et al[47]	1996, China	135	135	1.11 (0.67 to 1.84)			
Cohort studies							
Garfinkel[10]	1981, USA	153	176586	1.18 (0.90 to 1.54)			
Hirayama[16]	1984, Japan	200	91340	1.45 (1.02 to 2.08)	64	20225	2.25 (1.06 to 4.76)
Butler[31]	1988, USA	8	9199	2.02 (0.48 to 8.56)			
Cardenas et al[48]	1997, USA	150	192084	1.20 (0.80 to 1.60)	97	96445	1.00 (0.60 to 1.80)
All studies (37 studies of women, 9 studies of men)*							
	1981-97	4626	477924	1.24 (1.13 to 1.36) (P<0.001)	274	117260	1.34 (0.97 to 1.84) (P=0.07)

*In addition, there were two studies which gave results only for men and women combined: Hole et al,[32] (7 lung cancer cases) relative risk 2.14 (95% confidence interval 0.45 to 12.83); Janerich et al,[38] (188 lung cancer cases), relative risk 0.75 (0.48 to 1.18).

included studies comparing the risk of lung cancer in lifelong non-smokers according to whether the spouse (cohabitees are included in this term) currently smoked or had never smoked. There were five cohort and 34 case-control studies.[10-48] Twenty nine studies were in peer reviewed journals, four in books with an ISBN number, two in peer reviewed doctoral theses, and three in published proceedings of scientific conferences; one study was an official report from a scientific organisation. We excluded studies with fewer than five cases of lung cancer (too few to calculate an odds ratio),[49 50] those that did not report separate results in non-smokers (the proportionate effect of exposure to environmental tobacco smoke is much smaller in smokers),[51-58] and those that did not have controls[59] or had controls with smoking related diseases.[60] We excluded studies in which the effects of exposure to environmental tobacco smoke and radon could not be distinguished[61] and studies that were duplicate publications of the same cases.[62-69] We also excluded three studies in which exposure from a spouse and exposure outside the home were not distinguished[70-72] and one unpublished study that had been submitted to the United States Occupational Safety and Hygiene Authority[73]; inclusion of these four studies would have altered the summary relative risk estimate by less than 1%.

In 35 studies lung cancer was generally (86%) confirmed histologically or cytologically; in four it was not stated how it was diagnosed.[10 16 30 38] In the case-control studies controls were selected from the general population in 17 studies,[14 19 22-43 47 69] and from patients with non-smoking-related diseases in 17 studies.[1 12 13 15 17 18 20 21 27 29 30 33 34 41 42 44 45] Age in years was generally the same in cases and controls; the age adjusted estimate was used in three studies in which it

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Table 2 Relative risk of lung cancer and exposure to environmental tobacco smoke in the 39 epidemiological studies according to sex, geographical region, year of publication, and study design

	No of studies	No of lung cancer cases	Pooled relative risk (95% confidence interval)
By sex:			
Women	37	4626	1.24 (1.13 to 1.36)
Men	9	274	1.34 (0.97 to 1.84)
Both*	39	5095	1.23 (1.13 to 1.34)
By geographical region†:			
USA	14	1959	1.17 (1.05 to 1.31)
Europe‡	6	439	1.53 (1.21 to 1.94)
Japan	5	550	1.28 (1.04 to 1.57)
China and Hong Kong§	12	1678	1.22 (0.99 to 1.50)
By year of publication†:			
1981-5	10	809	1.29 (1.06 to 1.58)
1986-90	15	1591	1.28 (1.07 to 1.54)
1991-7	12	2226	1.19 (1.06 to 1.33)
By study design†:			
Case-control	33	4115	1.24 (1.12 to 1.38)
Cohort	4	511	1.27 (1.05 to 1.53)

*Including the two studies of men and women combined.[32 36]
†Studies of women only.
‡United Kingdom, Sweden, Greece, Russia.
§Excluding Wu-Williams et al,[35] the pooled estimate was 1.30 (95% confidence interval 1.09 to 1.56).

was not.[30 40 60] We used odds ratios unadjusted for potential confounding factors except in four studies, in which only adjusted estimates were available.[19 38 40 69] For the cohort studies we used the published age adjusted relative risks (and 95% confidence interval). The relative risk estimates from the studies were pooled using the method of DerSimonian and Laird,[74 75] which allows for heterogeneity between studies by weighting each study using the within and between study variance. If there is no heterogeneity, weighting is by the inverse of the variance (fixed effects).

Indirect estimate of risk by extrapolation from the risk in smokers

We estimated the risk of lung cancer in non-smokers exposed to environmental tobacco smoke by extrapolating from the risk in smokers, using the urine or saliva concentrations of cotinine and nicotine (both sufficiently tobacco specific) in each. A weighted average ratio was calculated from all such studies, identified using Medline.

Results

Table 1 shows details of the 39 (five cohort and 34 case-control) studies. Seven showed a significant excess risk. The pooled relative risk of lung cancer from the 37 studies on women was 1.24 (95% confidence interval 1.13 to 1.36) ($P < 0.001$)—a 24% excess risk among lifelong non-smokers with spouses who smoked. Inclusion of the nine studies of men and the two reporting only on men and women combined made little difference (pooled relative risk 1.23 (1.13 to 1.34)).

Heterogeneity

Table 2 shows that relative risk estimates of lung cancer and exposure to environmental tobacco smoke did not significantly differ between men and women ($P = 0.31$), between geographical regions ($P = 0.26$), with year of publication ($P = 0.16$), or between cohort and case-control studies ($P = 0.53$). There was heterogeneity across the studies of women ($P = 0.10$), the studies from China and Hong Kong ($P = 0.01$), the studies published between 1986 and 1990 ($P = 0.05$), and the case-control studies ($P = 0.06$), but this was entirely due to the inclusion of one study.[35] When this study was excluded there was no evidence of heterogeneity ($P > 0.20$). Its effect on the pooled relative risk estimate was negligible (1.24 with it, 1.26 without it). This study suggested an implausible protective effect from exposure to environmental tobacco smoke (relative risk 0.79 (0.62 to 1.02)). The authors commented that, in their study, the effect of environmental tobacco smoke was probably obscured by another cause of lung cancer, indoor cooking using open coal fires with little ventilation.[35]

The following results are based only on the 37 studies of women and exposure from their husbands (cohabitants again included) because most of the cases of lung cancer (91%) and most of the data necessary to quantify the effects of bias and confounding were in women.

Figure 1 is a cumulative plot of the pooled relative risk of lung cancer and exposure to environmental tobacco smoke in non-smokers from all studies available each year up to 1997. It shows that the addition of further studies over time has not materially changed the estimate, so our current estimate of 1.24 is robust.

Dose-response relation

Data on the dose-response relation between the number of cigarettes smoked by the husband and the risk of lung cancer was reported in 16 studies.[19 13 16 18 20 22 24 25 28 30 38 41 42 44 17 48] Figure 2(a) shows data from one such study[28] with a significant trend. For each study a linear regression analysis was performed

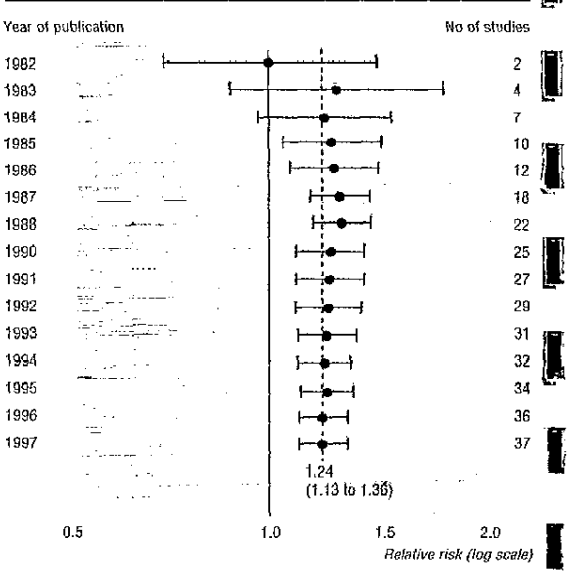

Fig 1 Cumulative pooled estimate of relative risk (bars show 95% confidence interval) of lung cancer from studies of women who were lifelong non-smokers living with a smoker compared with those living with a non-smoker. (Number of studies on which each pooled estimate is based is shown to right of figure)

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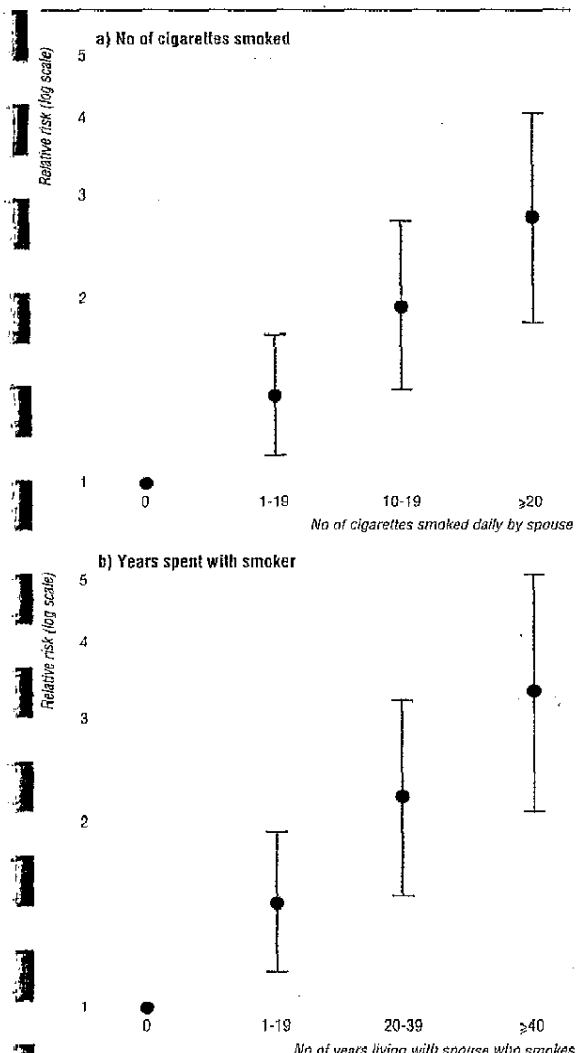

Fig 2 Dose-response relation between the relative risk (95% confidence interval) of lung cancer and (a) the number of cigarettes smoked daily by the spouse and (b) the number of years living with a spouse who smokes. (Data from study of Geng et al[28])

between the relative risk (in logarithms) and the number of cigarettes smoked by the husband. The summary estimate (allowing for the within and between study variation[74 76]) shows a significant dose-response relation. Risk increases by 23% (14% to 32%) for every 10 cigarettes smoked per day by the husband (88% if he smoked 30).

Eleven studies[14 20 24 26 28 33 40 41 43 47 48] examined risk according to the number of years a woman lived with a smoker. Figure 2(b) shows the results from one such study.[28] The summary estimate showed a significant increase in risk with increasing duration of exposure. Risk increases by 11% (4% to 17%) for every 10 years of exposure (35% for 30 years' exposure). These results were not dependent on constraining the regression line through the relative risk of 1.0 by the inclusion of women with spouses who did not smoke.

Histological type

Several studies reported on the histological type of lung cancer. The pooled relative risk was 1.58 (1.14 to 2.19) for squamous and small cell carcinoma[18 19 22 23 25 33 39 40 48 77] and 1.25 (1.07 to 1.46) for adenocarcinoma alone.[17-19 27 33 39 40 43] Smoking itself is more strongly related to squamous and small cell carcinoma than adenocarcinoma, so this difference, though not significant (P = 0.2), is consistent with the view that exposure to environmental tobacco smoke is equivalent to low dose smoking.

Biases and confounding in epidemiological studies

The excess risk of lung cancer in non-smokers who live with smokers has been claimed to be entirely attributable to bias.[77] We quantified two sources of bias and one source of confounding that may affect the relative risk of lung cancer in the studies.

Misclassification bias

Some current or former smokers may say that they are lifelong non-smokers and so be misclassified in the studies. Because of their smoking status, they are more likely to develop lung cancer, and because smokers tend to live with smokers this particular bias will overestimate the true risk of lung cancer.[5]

Misclassification bias increases with increasing values of four determinants: the prevalence of reported smoking among women; the extent to which women who smoke are more likely to have a husband who smokes (aggregation ratio); the proportion of women who had ever smoked who report themselves to be lifelong non-smokers; and the risk of lung cancer in misclassified ever smokers. The four determinants were estimated as follows:

Smoking prevalence was specified in individual studies; if it was not we used national data.

Aggregation ratio—Estimates of the aggregation ratio generally lie between 2 and 4.[5 14 20 32 78-86] We used an estimate of 3.

The proportion of ever smokers misclassified as never smokers was derived by adding two separate estimates of misclassified current and former smokers. The first is the proportion of all ever smokers who are current smokers misclassified as never smokers, which is 3.1% and is estimated as follows. Of reported non-smokers, 2.0% are likely to be current smokers from nicotine or cotinine concentrations (table 3). Of British women, 53% report that they are never smokers, 21% that they are former smokers, and 26% that they are current smokers.[98] Hence, 1.48% of all women are current smokers who report being never or former smokers (2.0% × (53% + 21%)); these are 3.1% of all ever smok-

Table 3 Cotinine and nicotine concentrations in reported non-smokers (never smoked and former smokers) as markers of probable current smoking

Study	Marker	No of reported non-smokers	No (%) of non-smokers with high concentrations*
Feyerabend et al[87]	Urinary nicotine	56	0 (0)
Wald et al[6]	Urinary cotinine	221	2 (0.9)
Pojer et al[88]	Plasma cotinine	181	6 (3.3)
Haddow et al[89]	Serum cotinine	232	3 (1.3)
Lee[85]	Salivary cotinine	808	20 (2.5)
Thompson et al[7]	Urinary cotinine	184	2 (1.1)
All		1682	33 (2.0)

*>10% of median or mean concentration in active smokers.

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Table 4 Sensitivity analysis of the effect of misclassification bias: relative risk (95% confidence interval) of lung cancer and exposure to environmental tobacco smoke in the epidemiological studies after adjusting for misclassification of smokers (past or present) as never smoking. (With no misclassification, relative risk is 1.24 (1.13 to 1.36))

Aggregation ratio*	% of ever smokers misclassified as never smokers	Relative risk of lung cancer in misclassified ever smokers		
		2	3	4
3	5	1.22 (1.11 to 1.34)	1.20 (1.08 to 1.32)	1.17 (1.06 to 1.30)
3	7	1.21 (1.10 to 1.33)	1.18 (1.06 to 1.30)†	1.14 (1.02 to 1.27)
3	9	1.20 (1.09 to 1.32)	1.15 (1.04 to 1.29)	1.11 (0.99 to 1.25)
4	5	1.21 (1.10 to 1.33)	1.19 (1.07 to 1.31)	1.16 (1.04 to 1.28)
4	7	1.20 (1.09 to 1.33)	1.16 (1.05 to 1.29)	1.12 (1.00 to 1.25)
4	9	1.19 (1.08 to 1.31)	1.13 (1.02 to 1.27)	1.08 (0.95 to 1.22)

*Aggregation ratio of 3, for example, means that a woman is 3 times more likely to smoke if her spouse smokes than if he does not.
†Estimate for Britain.

ers (1.48%/(21% + 26%)). The second is the proportion of all ever smokers who are former smokers misclassified as never smokers, which is 3.8% and is estimated from responses to surveys on smoking by the same people on two separate occasions as follows. In one study of 1296 never smokers, 851 former smokers, and 1127 current smokers, 102 of the smokers claimed to be never smokers at a subsequent interview some years later.[91] Therefore, 5.1% (102/(851 + 1127)) of ever smokers were former smokers who reported themselves as never smokers. In another study of similar size the estimate was 2.5%[92]; the average of these two estimates is 3.8%. The proportion of all ever smokers in Great Britain who are misclassified as never smokers is, therefore, about 7% (3.1% + 3.8%).

The relative risk of lung cancer in misclassified ever smokers was obtained separately for misclassified current and former smokers. Women who currently smoke but report themselves as never smokers tend to be light smokers; the cotinine concentrations in misclassified women in table 3 were about 30% of the mean or median concentration in reported active smokers. Their risk of lung cancer will be correspondingly low. The relative risk in women is 12 on average,[93] an 11-fold excess risk, so the excess risk in these women is 3.3 (30% × 11), and the relative risk is 4.3. Former smokers reporting to be never smokers are likely to have given up smoking long ago and to have smoked less than continuing smokers.[77] Most gave up at least 10 years previously (N Britten, personal communication), and even if they smoked 20 cigarettes a day their risk of lung cancer would only be about 1.5.[93] The estimated overall relative risk for misclassified current and former smokers together is therefore 3.0 (average of 4.3 and 1.5, weighted by the proportions of current (26%) and former (21%) smokers[90]).

These estimates of the determinants of misclassification bias are similar to those obtained in the previous analysis,[5] despite the additional data now available; they are therefore likely to be robust. The relative risk estimates from each of the 37 studies were adjusted for misclassification bias; the method, a modification of that used before,[5] is described in the appendix. Table 4 shows estimates of the overall adjusted relative risk estimate according to various combinations of the determinants of misclassification bias. Implausibly high values are required to reduce the observed relative risk of 1.24 to a value that is not significant. With the most likely values (listed above), the observed relative risk in the 37 studies of 1.24 (1.13 to 1.36) is reduced to 1.18 (1.06 to 1.30) ($P < 0.001$).

Bias due to exposure to environmental tobacco smoke in reference group

In the epidemiological studies the reference group—non-smoking women living with non-smokers—was taken to have no exposure and no increase in risk. Some of these women would have been exposed to environmental tobacco smoke from other sources. The average urinary cotinine in non-smokers with a non-smoking spouse is not zero,[6-9] yet nicotine from tobacco smoke is, for practical purposes, the only source of cotinine. This increase in risk in the reference group will dilute (reduce) the relative risk estimate.

This can be corrected by using data on urinary cotinine concentrations.[5] In four studies urinary cotinine concentration in non-smokers living with smokers was, on average, three times that in non-smokers living with non-smokers.[6-9] If x is the excess risk of lung cancer in non-smokers living with a non-smoker, then $3x$ is the excess risk in non-smokers living with a smoker. The observed relative risk (1.24) is equal to $(1 + 3x)/(1 + x)$, so $x = 0.14$. The risk in non-smokers living with a smoker relative to non-smokers with no exposure to environmental tobacco smoke (urinary cotinine zero) is thus $1 + 3x = 1.42$ (1.21 to 1.66).

Dietary confounding

In nine studies of women who had never smoked,[29 33 94-100] low fruit and vegetable consumption was associated with a higher risk of lung cancer, suggesting that nutrients in fruit and vegetables may protect against lung cancer. Smokers eat less of these foods than do non-smokers,[101-104] and non-smokers who live with smokers eat less of them than do non-smokers who live with non-smokers.[48 105-108] Part of their excess lung cancer risk could, therefore, arise through dietary confounding.

Most of the studies did not record data on diet, and we estimated its confounding effect indirectly. From a pooled regression analysis of the studies of fruit and vegetable consumption and lung cancer in non-smoking women, the relative risk associated with a decrease in consumption of one standard deviation was 1.20 (this corresponds to a relative risk of 1.5 in the quarter of the population with the lowest consumption compared with the quarter with the highest). The difference in the consumption of fruit and vegetables between non-smokers who do and do not live with smokers was estimated in three studies (about 185 000 non-smokers in total)[48 104 108]; the largest difference was −0.12 standard deviations. The relative risk of lung cancer corresponding to this difference is 1.02 (antilog (log 1.20 × 0.12)). Of the overall 24% excess risk of lung cancer in non-smokers exposed to environmental tobacco smoke, only 2% is accounted for by dietary differences. The estimated relative risk due to exposure to environmental tobacco smoke allowing for confounding is thus 1.21 (1.24/1.02). The eight epidemiological studies of exposure to environmental tobacco smoke and the risk of lung cancer that directly recorded data on diet confirmed the negligible effect of dietary confounding.[33 48 48 65 98 100 109]

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Table 5 Estimates of concentrations of nicotine and cotinine in urine and saliva of non-smokers, whether or not exposed to environmental tobacco smoke (ETS), and of smokers

Study	Non-smokers: Not exposed to ETS: No of subjects	Non-smokers: Not exposed to ETS: Mean concentration	Non-smokers: Exposed to ETS*: No of subjects	Non-smokers: Exposed to ETS*: Mean concentration	Smokers: No of subjects	Smokers: Mean concentration	Concentration in non-smokers exposed to smoke as percentage of concentration in smokers
Nicotine in urine (ng/ml)							
Feyerabend et al[87]	26	7.5	30	21.5	82	1227.0	1.8
Jarvis et al[112]	46	3.9	54	12.1	94	1749.9	0.7
Nicotine in saliva (ng/ml)							
Feyerabend et al[87]	26	5.9	30	10.0	82	502.9	2.0
Jarvis et al[112]	46	3.8	54	5.3	94	672.5	0.8
Cotinine in urine (ng/ml)							
Jarvis et al[112]	46	1.6	54	7.6	94	1391.0	0.5
Wald et al[113]	22	3.0	199	14.1	131	2005.6	0.7
Cummings et al[114]	162	6.2	501	9.5	130	1254.0	0.8
Thompson et al[7]	158	11.0	26	26.0	49	1691.0	1.7
Willers et al[9]	42	2.3	14	6.2	39	2600.0	0.2
Cotinine in saliva (ng/ml)							
Jarvis et al[112]	46	0.7	54	2.5	94	309.9	0.8
Jarvis et al[115]	89	0.3	299	0.7	306	129.9	0.6
All studies							1.0†

*People who reported exposure to environmental tobacco smoke from their spouse and outside their home.
†Weighted average of the ratios by the number of non-smokers exposed to environmental tobacco smoke plus the number of smokers.

Overall estimate of risk of lung cancer

Adjustment of the observed relative risk of 1.24 (1.13 to 1.36) for misclassification bias reduced it to 1.18 (1.07 to 1.31); adjustment for dietary confounding further reduced it to 1.16 (1.04 to 1.27), but adjustment for exposure to environmental tobacco smoke in the reference group increased it to 1.26 (1.06 to 1.47). The effects tend to cancel, and the unadjusted (observed) pooled relative risk is a valid estimate of the true risk.

Indirect estimate of risk of lung cancer by extrapolation from the risk in smokers

The relative risk of lung cancer in men who currently smoke compared with never smokers is about 20 (excess risk 19).[93 110] (The lower risk in women reflects fewer years of smoking, but they have been exposed to environmental tobacco smoke from men for longer.) The relation between the intake of tobacco smoke and the risk of lung cancer is quadratic, but it is almost linear up to about 25 cigarettes a day.[111] It is, therefore, possible to estimate the risk due to exposure to environmental tobacco smoke by linear extrapolation.

Table 5 summarises the results of seven studies measuring the urine or saliva concentration of nicotine and cotinine. In non-smokers exposed to environmental tobacco smoke, marker concentrations are about 1.0% of those in smokers. As cotinine and nicotine are tobacco specific, non-smokers exposed to environmental tobacco smoke have about 1% of the exposure to tobacco smoke of smokers and therefore 1% of the excess risk of lung cancer—19% (1% of 19). This is similar to the estimate of 20% from a low dose extrapolation based on an analysis of pooled data from nine large cohort studies of the risk of lung cancer according to cigarette consumption.[116] The indirect (19%) and direct (26%) estimates of excess risk are similar.

Discussion

Carcinogens in environmental tobacco smoke are inhaled and pass into the blood. Experimental exposure of non-smokers to tobacco smoke increased the urinary concentration of a tobacco specific carcinogen,[117] and non-smokers exposed to environmental tobacco smoke have raised blood concentrations of tobacco specific carcinogen adducts—for example, DNA and haemoglobin adducts.[118-121] It is therefore to be expected that exposure to environmental tobacco smoke causes cancer.

This analysis compared with the previous one[5] uses three times as many studies (37 *v* 13), with seven times as many cases of lung cancer (4626 *v* 676). The pooled estimate of the excess risk (24%) is more precise (95% confidence interval 13% to 36%). Despite additional data on the two sources of bias, the previous estimates of their size did not materially change, and are therefore robust.[5] Bias and confounding do not explain the effect, and the adjusted estimate of the excess risk was 26%. The finding of a significant dose-

Key messages

- A woman who has never smoked has an estimated 24% greater risk of lung cancer if she lives with a smoker
- Neither bias nor confounding accounted for the association
- There is a dose-response relation between a non-smoker's risk of lung cancer and the number of cigarettes and years of exposure to the smoker
- The increased risk was consistent with that expected from extrapolation of the risk in smokers using biochemical markers
- Tobacco specific carcinogens are found in the blood and urine of non-smokers exposed to environmental tobacco smoke
- All the available evidence confirms that exposure to environmental tobacco smoke causes lung cancer

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response relation between the risk of lung cancer and the extent of exposure to environmental tobacco smoke adds weight to the evidence that the association between exposure and lung cancer is causal.

There was no evidence of publication bias against negative studies. Seven studies found a significant ($P<0.05$) positive result. If there were no association, the probability of such a result arising by chance is 1 in 40, so a total of 280 studies (7×40) would be required to generate the seven significant ones. It is implausible that there should be as many as 241 unpublished studies to 39 published ones.

The similarity of the direct estimate of lung cancer due to environmental tobacco smoke and the indirect estimate from extrapolating from the risk in smokers, the evidence of a dose-response relation, the inability of bias or confounding to explain the association, and the presence of tobacco specific carcinogens in the blood and urine of non-smokers lead to an inescapable conclusion that exposure to environmental tobacco smoke is a cause of lung cancer. The estimated excess risk of 26% corresponds to several hundred deaths per year in Great Britain. Our review corroborates and strengthens earlier conclusions that environmental tobacco smoke causes lung cancer.

Appendix

Adjustment for misclassification bias

The method used to adjust for misclassification bias was that previously used[5] with two modifications (P Lee, personal communication, 1986). The proportion of true ever smokers misclassified as never smokers was used; previously it was applied to reported ever smokers, and the risk of lung cancer in misclassified smokers was expressed relative to that in all reported non-smokers; previously it was relative to true non-smokers married to non-smokers. The difference in results is minor. In the previous analysis[5] the relative risk adjusted for misclassification was 1.30; with the modification, the estimate was 1.28.

The method involves first obtaining estimates of the proportions of individuals in a population according to the reported and true smoking statuses of husbands and wives (table A1). The values S_1, S_2, N_1, N_2, s_1, s_2, n_1, and n_2 can be estimated using (*a*) the aggregation ratio $C=(S_1\times N_2)/(S_2\times N_1)$ (our best estimate was $C=3$) and (*b*) the proportion of true female ever smokers misclassified as never smokers (D), where $S_1=(1-D)\times s_1$ and $S_2=(1-D)\times s_2$, (our best estimate was $D=7\%$).

Table A2 shows the proportion of women who are reported non-smokers according to their true smoking status and their risk of lung cancer. The observed relative risk from each study (RR_{obs}) and the relative risk in smoking women who are misclassified as non-smokers compared with all reported non-smokers (RR_{mis}) are known (see box).

$$RR_{obs}=\frac{(n_1(1+R_1)+(N_1-n_1)(1+E_1+E_2))/N_1}{(n_2\times1+(N_2-n_2)(1+E_2))/N_2}$$

$$RR_{mis}=\frac{((N_2-n_2)(1+E_2)+(N_1-n_1)(1+E_1+E_2))/(N_2-n_2+N_1-n_1)}{(n_2\times1+n_1(1+E_1)+(N_2-n_2)(1+E_2)+(N_1-n_1)(1+E_1+E_2))/(N_1+N_2)}$$

Table A1 Proportion of individuals in population according to reported and true smoking statuses of husbands and wives

	Wife		
Husband	Ever smoker	Never smoker	Total
Ever smoker	S_1 (s_1)	N_1 (n_1)	A
Never smoker	S_2 (s_2)	N_2 (n_2)	1–A
Total	B	1–B	1

S_1, S_2, N_1, N_2, A, and B refer to the reported smoking status and s_1, s_2, n_1, and n_2 to the true smoking status; A is the proportion of reported male smokers, and B is the proportion of reported female smokers.

Table A2 Proportion of women who are reported non-smokers according to their true smoking status and risk of lung cancer

Wife's smoking habits				
Reported	True	Husband	Proportion of women	Relative risk
Non-smoker	Non-smoker	Non-smoker	n_2	1
Non-smoker	Non-smoker	Smoker	n_1	$1+E_1$
Non-smoker	Smoker	Non-smoker	N_2-n_2	$1+E_2$
Non-smoker	Smoker	Smoker	N_1-n_1	$1+E_1+E_2$

E_1 and E_2 are the excess risks.

The equations for RR_{obs} and RR_{mis} simplify to two simultaneous equations from which the values of E_1 and E_2 can be calculated. $1+E_1$ is then the relative risk of lung cancer due to exposure to environmental tobacco smoke in true non-smoking women. The standard error of the adjusted relative risk was obtained by adjusting the upper 95% confidence limit for the observed (unadjusted) relative risk in the same way as described above. The adjusted relative risks were then pooled as before.[25]

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1 National Research Council. *Environmental tobacco smoke: measuring exposures and assessing health effects.* Washington, DC: National Academy Press, 1986.
2 US Department of Health and Human Services. The health consequences of involuntary smoking. A report of the surgeon general. Washington, DC: DHHS, 1986. (Publication No (PHS) 87-8398.)
3 UK Department of Health and Social Security. *Fourth report of the independent scientific committee on smoking and health.* London: HMSO, 1988.
4 Australian National Health and Medical Research Council. *Effects of passive smoking on health. Report of the NHMRC Working Party on the effects of passive smoking on health.* Canberra: Australia Government Publishing Service, 1987.
5 Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does breathing other people's tobacco smoke cause lung cancer? *BMJ* 1986;293:1217-22.
6 Wald NJ, Ritchie C. Validation of studies on lung cancer in nonsmokers married to smokers. *Lancet* 1984;i:1067.
7 Thompson SG, Stone R, Nanchahal K, Wald NJ. Relation of urinary cotinine concentrations to cigarette smoking and to exposure to other people's smoke. *Thorax* 1990;45:356-61.
8 Riboli E, Preston-Martin S, Saracci R, Haley NJ, Trichopoloulos D, Becher H, et al. Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study. *Cancer Causes and Control* 1990;1:243-52.
9 Willers S, Attewell R, Bensryd I, Schultz A, Skarping G, Vahter M. Exposure to environmental tobacco smoke in the household and urinary cotinine excretion, heavy metals retention and lung function. *Arch Environ Health* 1992;47:357-63.
10 Garfinkel L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J Natl Cancer Inst* 1981;66:1061-6.
11 Chan WC, Fung SC. Lung cancer in non-smokers in Hong Kong. In: Grundmann E, ed. *Cancer campaign. Vol 6. Cancer epidemiology.* New York: Gustav Fischer, 1982:199-202.
12 Correa P, Pickle LW, Fontham E, Lin Y, Haenszel W. Passive smoking and lung cancer. *Lancet* 1983;ii:595-7.
13 Trichopoulos D, Kalandidi A, Sparros L. Lung cancer and passive smoking: conclusion of the Greek study. *Lancet* 1983;ii:677-8.

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14 Buffler PA, Pickle LW, Mason TJ, Contant C. The causes of lung cancer in Texas. In: Mizell M, Correa P, eds. *Lung cancer causes and prevention*. New York: Verlag Chemie International, 1984:83-99.
15 Kabat GC, Wynder EL. Lung cancer in nonsmokers. *Cancer* 1984;53:1214-21.
16 Hirayama T. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev Med* 1984;13:680-90.
17 Lam WK. *A clinical and epidemiological study of carcinoma of the lung in Hong Kong*. Hong Kong: University of Hong Kong, 1985. (PhD thesis.)
18 Garfinkel L, Auerbach O, Joubert L. Involuntary smoking and lung cancer: a case-control study. *J Natl Cancer Inst* 1985;75:463-9.
19 Wu A, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. *J Natl Cancer Inst* 1985;74:747-9.
20 Akiba S, Kato H, Blot WJ. Passive smoking and lung cancer among Japanese women. *Cancer Res* 1986;46:4804-7.
21 Lee PN, Chamberlain J, Alderson MR. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *Br J Cancer* 1986;54:97-105.
22 Koo LC, Ho JHC, Saw D, Ho C. Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. *Int J Cancer* 1987;39:162-9.
23 Pershagen G, Hrubec Z, Svensson C. Passive smoking and lung cancer in Swedish women. *Am J Epidemiol* 1987;125:17-24.
24 Humble CG, Samet JM, Pathak DR. Marriage to a smoker and lung cancer risk. *Am J Public Health* 1987;77:5989-602.
25 Lam TH, Kung HM, Wong CM, Lam WK, Kleevens JWL, Saw D, et al. Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. *Br J Cancer* 1987; 56:673-8.
26 Gao Y-T, Blot WJ, Zheng W, Ershow AG, Hsu CW, Levin LI, et al. Lung cancer among Chinese women. *Int J Cancer* 1987;40:604-9.
27 Brownson RC, Reif JS, Keefe TJ, Ferguson SW, Pritzl JA. Risk factors for adenocarcinoma of the lung. *Am J Epidemiol* 1987;125:25-34.
28 Geng G, Liang ZH, Zhang AY, Wu GL. On the relationship between smoking and female lung cancer. In: Aoki M, Hisamichi S, Tominaga S, eds. *Smoking and health*. Amsterdam: Elsevier Science, 1988:483-6.
29 Shimizu H, Morishita M, Mizuno K, Masuda T, Ogura Y, Santo M, et al. A case-control study of lung cancer in non-smoking women. *Tohoku J Exp Med* 1988;154:389-97.
30 Inoue R, Hirayama T. Passive smoking and lung cancer in women. In: Aoki M, Hisamichi S, Tominaga S, eds. *Smoking and health*. Amsterdam: Elsevier Science, 1988:283-5.
31 Buter TL. *The relationship of passive smoking to various health outcomes among Seventh-Day Adventists in California*. University of California: Los Angeles, 1988. (Dissertation.)
32 Hole DJ, Gillis GR, Chopra C, Hawthorne VM. Passive smoking and cardiorespiratory health in a general population in the west of Scotland. *BMJ* 1989;299:423-7.
33 Kalandidi A, Katsouyanni K, Voropoulou N, Bastas G, Saracel R, Trichopolous D. Passive smoking and diet in the etiology of lung cancer among non-smokers. *Cancer Causes and Control* 1990;1:15-21.
34 Sobue T. Association of indoor air pollution and lifestyle with lung cancer in Osaka, Japan. *Int J Epidemiol* 1990;19:S62-6.
35 Wu-Williams AH, Dai XD, Blot W, Xu ZY, Sun XW, Xiao HP, et al. Lung cancer among women in north-east China. *Br J Cancer* 1990;62:982-7.
36 Janerich DT, Thompson WD, Varela LR, Greenwald P, Chorost S, Tucci C, et al. Lung cancer and exposure to tobacco smoke in the household. *N Engl J Med* 1990;323:632-6.
37 Liu Z, He X, Chapman RS. Smoking and other risk factors for lung cancer in Xuanwei, China. *Int J Epidemiol* 1991;20:26-31.
38 Jockel K-H. Passive smoking—evaluation of the epidemiological findings. Presentation to the Association of German Engineers, Mannheim colloquium, April 1991. Dusseldorf: Verein Deutscher Ingenieure, 1991. (VDI reports 888.)
39 Brownson RC, Alavanja MCR, Hock ET, Loy TS. Passive smoking and lung cancer in nonsmoking women. *Am J Public Health* 1992;82:1525-30.
40 Stockwell HG, Goldman AL, Lyman GH, Noss CI, Armstrong AW, Pinkham PA, et al. Environmental tobacco smoke and lung cancer risk in nonsmoking women. *J Natl Cancer Inst* 1992;84:1417-22.
41 Du YX, Cha Q, Chen YZ, Wu JM. Exposure to environmental tobacco smoke and female lung cancer in Guangzhou, China. *Proceedings of Indoor Air* 1993;1:511-6.
42 Liu Q, Sasco AJ, Riboli E, Hu MX. Indoor air pollution and lung cancer in Guangzhou, People's Republic of China. *Am J Epidemiol* 1993;137:145-54.
43 Fontham ETH, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. *JAMA* 1994;271:1752-9.
44 Kabat GC, Stellman SD, Wynder EL. Relation between exposure to environmental tobacco smoke and lung cancer in lifetime nonsmokers. *Am J Epidemiol* 1995;142:141-8.
45 Zaridze DG, Zemlianaia GM, Aitakov ZN. Role of outdoor and indoor air pollution in the etiology of lung cancer [in Russian]. *Vestn Ross Akad Med Nauk* 1995;4:6-10.
46 Sun X-W, Dai X-D, Lin C-Y, Shi Y-B, Ma Y-Y, Li W. Passive smoking and lung cancer among nonsmoking women in Harbin, China. International symposium on lifestyle factors and human lung cancer, China 1994. *Lung Cancer* 1996;14:S237.
47 Wang T-J, Zhou B-S, Shi J-P. Lung cancer in nonsmoking Chinese women: a case-control study. International symposium on lifestyle factors and human lung cancer, China 1994. *Lung Cancer* 1996;14:S93-8.
48 Cardenas VM, Thun MJ, Austin H, Lally CA, Clark WS, Greenberg S, et al. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's cancer prevention study II. *Cancer Causes Control* 1997;8:57-64.
49 Sandler DP, Everson RB, Wilcox AJ. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 1985;121:37-48.
50 Katada H, Mikami R, Konishi M, Koyama Y, Narita N. Effect of passive smoking in lung cancer development in women in the Nara region. *Gan No Rinsho* 1988;34:21-7.
51 Lloyd OL, Ireland E, Tyrrell H, Williams F. Respiratory cancer in a Scottish industrial community: a retrospective case-control study. *J Soc Occup Med* 1986;36:2-8.
52 Li WX, Yang X, Mei YL. A case control study of female lung cancer at Xuhui District in Shanghai. *Chin J Prev Med* 1989;23:93-5.
53 Ye Z, Wang QY. The environmental factors of lung cancer in family women, Tianjin. *Chin J Clin Oncol* 1990;17:195-8.
54 Holowaty EJ, Risch HA, Miller AB, Burch JD. Lung cancer in women in the Niagara region Ontario: a case-control study. *Can J Public Health* 1991;82:304-9.
55 Ger LP, Hsu WL, Chen KT, Chen CJ. Risk factors of lung cancer by histological category in Taiwan. *Anticancer Res* 1993;13:1491-500.
56 Ye SZ, Zhao N. Combined analysis of case-control studies of smoking and lung cancer in China. *Lung Cancer* 1994;14(suppl 1):S161-70.
57 Lam Q, Chen W, Chen H, He XZ. Risk factors for lung cancer in non-smokers in Xuanwei County of China. *Biomed Environ Sci* 1993;6:112-8.
58 Luo R-X, Wu B, Yi Y-N, Huang Z-W, Lin R-T. Indoor burning coal air pollution and lung cancer—a case-control study in Fuzhou, China. International symposium on lifestyle factors and human lung cancer, China 1994. *Lung Cancer* 1996;14:S113-20.
59 Knoth A, Bohn H, Schmidt F. Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen. *Medizinische Klinik* 1983;78:54-9.
60 Miller GH, Golish JA, Cox CE, Chacko DC. Women and lung cancer: a comparison of active and passive smokers with nonexposed nonsmokers. *Cancer Detect Prev* 1994;18:421-30.
61 Axelson O, Andersson K, Desai G, Fagerlund I, Jansson B, Karlsson C, et al. Indoor radon exposure and active and passive smoking in relation to the occurrence of lung cancer. *Scand J Work Environ Health* 1988;14:286-92.
62 Hirayama T. Non smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *BMJ* 1981;282:183-5.
63 Trichopoulos D, Kalandidi A, Sparos L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer* 1981;27:1-4.
64 Gillis CR, Hole DJ, Hawthorne VM, Boyle P. The effects of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur J Respir Dis* 1984;65(suppl 133):121-6.
65 Dalager NA, Pickle LW, Mason TJ, Correa P, Fontham ETH, Stemhagen A, et al. The relation of passive smoking to lung cancer. *Cancer Res* 1986;46:4808-11. (Uses data from Correa et al[12] and Buffler et al.[14])
66 Lam TH, Cheng KK. Passive smoking is a risk factor for lung cancer in never smoking women in Hong Kong. In: Aoki M, Hisamichi S, Tominaga S, eds. *Smoking and health, 1987*. Amsterdam: Elsevier Science, 1988.
67 Kabat GC. Epidemiological studies of the relationship between passive smoking and lung cancer. Presentation on the American health foundation study. Proceedings of the winter toxicology forum, Washington, 1990. Washington: Toxicology Forum, 1990:187-99.
68 Fontham ETH, Correa P, Wu-Williams A, Reynolds P, Greenberg RS, Buffler PA, et al. Lung cancer in nonsmoking women: A multicenter case-control study. *Cancer Epidemiol Biomarker Prev* 1991;1:35-43.
69 Wang F-L, Love EJ, Liu N, Dai X-D. Childhood and adolescent passive smoking and the risk of female lung cancer. *Int J Epidemiol* 1994;23:223-30.
70 Svensson C, Pershagen G, Klominek J. Smoking and passive smoking in relation to lung cancer in women. *Acta Oncologica* 1989;28:623-9.
71 Shen X-B, Wang G-X, Huang Y-Z, Xiang L-S, Wang X-H. Analysis and estimates of attributable risk factors for lung cancer in Nanjing, China. International symposium on lifestyle factors and human lung cancer, China 1994. *Lung Cancer* 1996;14:S107-12.
72 Wang SY, Hu YL, Wu YL, Li X, Chi GB, Chen Y, et al. A comparative study of the risk factors for lung cancer in Guangdong, China. International symposium on lifestyle factors in human lung cancer. *Lung Cancer* 1996;14:S99-105.
73 Layard M. Ischaemic heart disease, lung cancer, and spousal smoking in the National mortality followback survey. Submitted to US Occupational Safety and Health Administration about proposed rules in the Federal Register, Vol 5 (No 65, docket No H-122, 1994).
74 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986;7:177-88.
75 Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat Med* 1991;10:1665-77.
76 Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. *Epidemiology* 1993;4:218-28.
77 Lee PN. *Environmental tobacco smoke and mortality*. Karger: Basle, 1992. (Uses data from Lee et al.[21])
78 De Mouzon J, Spira A, Schwartz D. A prospective study of the relation between smoking and fertility. *Int J Epidemiol* 1988;17:378-84.
79 Forastiere F, Agabiti N, Dell'Orco V, Pistelli R, Corbo GM, Brancato G, et al. Questionnaire data as predictors of urinary cotinine levels among nonsmoking adolescents. *Arch Environ Health* 1993;48:230-4.
80 Burchfiel CM, Higgins MW, Keller JB, Howatt WF, Buder WJ, Higgins ITT. Passive smoking in childhood. *Am Rev Respir Dis* 1986;133:966-73.
81 Ferris BG, Ware JH, Berkey CS, Dockery DW, Spiro A, Speizer FE. Effects of passive smoking on health of children. *Environ Health Perspectives* 1985;62:289-95.
82 Rona RJ, Chinn S, du ve Florey C. Exposure to cigarette smoking and children's growth. *Int J Epidemiol* 1985;14:402-8.
83 Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM. Effects on birth weight and smoking, alcohol, caffeine, socioeconomic factors and psychosocial stress. *BMJ* 1989;298:795-801.

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84 Ogston SA, du ve Florey C, Walker CHM. Association of infant alimentary and respiratory illness with parental smoking and other environmental factors. *J Epidemiol Community Health* 1987;41:21-5.
85 Lee PN. Passive smoking and lung cancer association: a result of bias? *Human Toxicol* 1987;6:517-24.
86 Sutton GC. Assortative marriage for smoking habits. *Ann Hum Biol* 1980;7:449-56.
87 Feyerabend C, Higenbottam T, Russell MAH. Nicotine concentrations in urine and saliva of smokers and nonsmokers. *BMJ* 1982;284:1002-4.
88 Pojer R, Whitfield JB, Poulous V, Eckhard IF, Richmond R, Hensley WJ. Carboxyhemoglobin, cotinine and thiocyanate assay compared for distinguishing smokers from non-smokers. *Clin Chem* 1984;30:1377-80.
89 Haddow JE, Palomaki GE, Knight GJ. Use of serum cotinine to assess the accuracy of self reported non-smoking. *BMJ* 1986;293:1306.
90 Office of Population Censuses and Surveys. *Living in Britain: results from the 1994 general household survey*. London: HMSO, 1996.
91 Britton N. Validity of claims to lifelong nonsmoking at age 36 in a longitudinal study. *Int J Epidemiol* 1988;17:525-9.
92 Hebert L, Fry JS. A report on a further analysis of the association between smoking behaviour, total mortality and cardiorespiratory disease in West Central Scotland. (Unpublished study, but results given in Lee.[77])
93 Shopland DR, Eyre HJ, Pechacek TF. Smoking attributable cancer mortality in 1991: is lung cancer now the leading cause of death among smokers in the United States? *J Natl Cancer Inst* 1991;83:1142-8.
94 Koo LC. Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. *Nutr Cancer* 1988;11:155-72.
95 Hirayama T. Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P, eds. *Lung cancer: causes and prevention. Proceedings of the international lung cancer update conference*. New Orleans, LA: Verlag Chemie International, 1984:175-95. (Uses data from Hirayama[10].)
96 Candelora EC, Stockwell HG, Armstrong AW, Pinkham P. Dietary intake and risk of lung cancer in women who never smoked. *Nutr Cancer* 1992;17:263-70.
97 Goodman MT, Violonel LN, Wilkens LR, Yoshizawa CN, Le Marchand L, Hankin JH. Dietary factors in lung cancer prognosis. *Eur J Cancer* 1992;28:495-501.
98 Alavanja MCR, Brown CC, Swanson C, Brownson RC. Saturated fat intake and lung cancer risk among nonsmoking women in Missouri. *J Natl Cancer Inst* 1993;85:1906-16. (Uses data from Brownson et al.[39])
99 Steinmetz KA, Potter JD, Folsom AR. Vegetables, fruits and lung cancer in the Iowa Women's health study. *Cancer Research* 1993;53:536-43.
100 Mayne ST, Janerich DT, Greenwald P, Chorost S, Tucci C, Zaman MB, et al. Dietary beta carotene and lung cancer risk in US nonsmokers. *J Natl Cancer Inst* 1994;86:33-8. (Uses data from Janerich et al.[36])
101 Hebert JR, Kabat GC. Differences in dietary intake associated with smoking status. *Eur J Clin Nutr* 1990;44:185-93.
102 McPhillips JB, Eaton CB, Gans KM, Derby CA, Lasater TM, McKenney JL, Carleton RA. Dietary differences in smokers and nonsmokers from two southeastern New England communities. *J Am Diet Assoc* 1994;94:287-92.
103 Margetts BM, Jackson AA. Interactions between people's diet and their smoking habits: the dietary and nutritional survey of British adults. *BMJ* 1993;307:1381-4.
104 Thornton A, Lee P, Fry J. Differences between smokers, ex-smokers, passive smokers and non-smokers. *J Clin Epidemiol* 1994;47:1143-62.
105 Sidney S, Caan BJ, Friedman GD. Dietary intake of carotene in nonsmokers with and without passive smoking at home. *Am J Epidemiol* 1989;129:1305-9.
106 Le Marchand L, Wilkens LR, Hankin JH, Haley NJ. Dietary patterns of female nonsmokers with and without exposure to environmental tobacco smoke. *Cancer Causes Control* 1991;2:11-6.
107 Tribble DL, Giuliano LJ, Fortman SP. Reduced plasma ascorbic acid concentrations in nonsmokers regularly exposed to environmental tobacco smoke. *Am J Clin Nutr* 1993;58:886-90.
108 Matanoski G, Kanchanaraska S, Lantry D, Chang Y. Characteristics of nonsmoking women in NHANES I and NHANES I epidemiologic follow-up study with exposure to spouses who smoke. *Am J Epidemiol* 1995;142:149-57.
109 Hirayama T. Dietary habits are of limited importance in influencing the lung cancer risk among Japanese females who never smoked. In: Bieva CJ, Courtois Y, Govaerts M, eds. *Present and future of indoor air quality. Proceedings of the Brussels conference, February 1989*. Amsterdam: Elsevier Science, 1989. (Uses data from Hirayama.[10])
110 Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observation on male British doctors. *BMJ* 1994;309:901-11.
111 Law MR, Morris JK, Watt HC, Wald NJ. The dose-response relationship between cigarette consumption, biochemical markers and risk of lung cancer. *Br J Cancer* 1997;75:1690-5.
112 Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Salloojee Y. Biochemical markers of smoke absorption and self reported exposure to passive smoking. *J Epidemiol Community Health* 1984;38:335-9.
113 Wald NJ, Boreham J, Bailey A, Ritchie C, Haddow JE, Knight G. Urinary cotinine as marker of breathing other people's tobacco smoke. *Lancet* 1984;i:230-1.
114 Cummings KM, Markello SJ, Mahoney M, Bhargava AK, McElroy PD, Marshall JR. Measurement of current exposure to environmental tobacco smoke. *Arch Environ Health* 1990;45:74-9.
115 Jarvis MJ, McNeill AD, Bryant A, Russell MAH. Factors determining exposure to passive smoking in young adults living at home: quantitative analysis using saliva cotinine concentrations. *Int J Epidemiol* 1991;20:126-31.
116 Puntoni R, Toninelli F, Zhankui L, Bonassi S. Mathematical modelling in risk/exposure assessment of tobacco related lung cancer. *Carcinogenesis* 1995;16:1465-71.
117 Hecht SS, Carmella SG, Murphy SE, Akerkar S, Brunnemann KD, Hoffman D. A tobacco-specific lung carcinogen in the urine of men exposed to cigarette smoke. *N Engl J Med* 1993;329:1543-6.
118 Madure M, Ben-Abraham R, Bryant MS, Skipper PL, Tannenbaum SR. Elevated blood levels of carcinogens in passive smokers. *Am J Public Health* 1989;79:1381-4.
119 Bartsch H, Caporaso N, Coda M, Kadlubar F, Malaveille C, Skipper P, et al. Carcinogen haemoglobin adducts, urinary mutagenicity and metabolic phenotype in active and passive cigarette smokers. *J Natl Cancer Inst* 1990;82:1826-31.
120 Hammond SK, Coghlin J, Gann PH, Paul M, Taghizadeh K, Skipper PL, et al. Relationship between environmental tobacco smoke exposure and carcinogen-hemoglobin adduct levels in nonsmokers. *J Natl Cancer Inst* 1993;85:474-8.
121 Crawford FG, Mayer J, Santella RM, Cooper TB, Ottman R, Tsai W-Y, et al. Biomarkers of environmental tobacco smoke in preschool children and their mothers. *J Natl Cancer Inst* 1994;86:1398-1402.

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A memorable patient

The father of the chapel

In the bad old days of heavy visiting I inherited this old couple from my senior partner. I was never sure of my role, except that I visited monthly. She was a short, fat, unpleasant woman, and he was gaunt and craggy, and very deaf. So deaf that he used an ear trumpet, despite my extolling the virtues of the then new NHS hearing aids. The household was made up with their 60 plus year old son and a small aggressive dog, which was the only beast that nipped me in some 38 years.

One day, I got a call to visit Dad, aged 92, as he had chest pain. I got there quickly, just before lunch time. Sure enough, he'd had a myocardial infarct and I discussed the management with his son. To be aggressive or not? To admit to hospital or not? We decided on a small dose of morphine, and I would revisit in a couple of hours which I did.

I made another visit on my way to the surgery, and by this time he was not improving, but he was not in pain either. On my way home from the surgery, he was sinking; his son wished to keep him at home, and his wife complained of a tight chest pain herself. The son confirmed that he wanted his father to stay at home and expressed satisfaction that his father was in no pain and comfortable in his own bed.

Father died at 10 pm and Mother died at 11 pm.

Father's obituary in the *Manchester Evening News* was fulsome—nine column inches all about "our oldest retired compositor" and "our oldest father of the chapel." "Sixty five wonderful years married," and so on.

His son later confided that it was typical of his mother that she would not even let her husband take centre stage on his deathbed. She was, in his words, "a horror," and his Dad used his ear trumpet so that he could remove it and have some peace.

The couple died in 1970 and their son died in 1976. He never married and had no children.

Stanley Goodman, *general practitioner, Manchester*

We welcome filler articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from a patient or a relative if an identifiable patient is referred to.

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